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Anlotinib Maintenance Following Adjuvant Chemotherapy in Newly Diagnosed Stage III–IV Patients with Epithelial Ovarian Cancer: A Retrospective Study

Jianghua Ding*, Zhaohui Leng

Department of Hematology and Oncology, The Affiliated Hospital of Jiujiang University, China

ABSTRACT

Background and Aims: Anti-angiogenesis therapy with bevacizumab maintenance marginally improved the median progression-free survival (mPFS) of 4.9 months in patients with advanced epithelial ovarian cancer (EOC). Anlotinib, an oral small-molecular anti-angiogenic agent, has been reported to treat platinum-resistant EOC. However, little is known about anlotinib maintenance therapy in newly diagnosed EOC.

Methods: This retrospective study included 20 patients with newly diagnosed EOC from a single hospital between January 2020 and December 2021. The primary endpoints were mPFS, the overall response rate (ORR), and the Disease Control Rate (DCR). Adverse reactions to therapy were also assessed.

Results: Among all EOC patients, the ORR was 65% (13/20) and the DCR was 95% (19/20), while the mPFS was 14.8 months (95% confidence interval, 11.5–18.0 months). Subgroup analysis revealed a trend toward a prolonged PFS among EOC patients with a wild-type status compared to those harboring BRCA1/2 mutations (14.8 vs. 11.8 months, P=0.3621). Seven patients (35%) required a dose reduction because of grade 3 or 4 adverse events, which were manageable and tolerable. No anlotinib-related death events were observed.

Conclusion: First-line anlotinib maintenance following adjuvant chemotherapy might be a novel therapeutic strategy, especially for BRCA wild-type EOC patients.

Keywords: Anlotinib; Maintenance therapy; Newly diagnosed; Ovarian cancer

INTRODUCTION

According to cancer statistics, ovarian cancer has become a female reproductive malignancy that severely threatens women's health. Ovarian cancer is the second leading cause of cancer-related death in women among gynecologic malignancies in China. An estimated 57,090 new cases and 39,306 deaths are expected in China in 2022, which is more than twice the number of cases expected in the United States [1]. Due to the insidious onset of ovarian cancer, >70% of patients is diagnosed at their first visit in an advanced stage of the disease. The present standard clinical treatment for advanced ovarian cancer includes primary debulking surgery, followed by platinum-based adjuvant chemotherapy. However, >75% of patients will relapse within 2 years of diagnosis and progressively develop treatment resistances [2]. Of note, the relapse-free interval is the key indicator for ovarian cancer survival following completion of the recommended cycles of chemotherapy; this is also known as the "platinum-free interval," i.e., the length of time from the last

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Corresponding author Jianghua Ding, Department of Hematology and Oncology, The Affiliated Hospital of Jiujiang University, China, E-mail: doctor0922@vip.126.com

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platinum-based cycle to the time of disease progression [3]. Therefore, extending the platinum-free interval may change the passive act of waiting for recurrence into active prophylactic treatment, which has become a topic of interest in the research on ovarian cancer in recent years.

The National Comprehensive Cancer Network (NCCN) guideline recommends first-line maintenance therapy using poly-ADP-ribose polymerase (PARP) inhibitors, including olaparib, or niraparib monotherapy for those with stage III–IV ovarian cancer following completion of the recommended cycles of chemotherapy [4]. However, until 2021, PARP inhibitors like olaparib were covered by the Chinese national health insurance system only for those with BRCA1/2 mutations. Thus, they have not been widely used in China due to the high cost of PARP inhibitors before 2021. In 2020, anti-angiogenesis therapy with bevacizumab was recommended as a maintenance treatment in ovarian cancer patients by the Chinese Anti-cancer Association and NCCN guidelines, but bevacizumab maintenance therapy only extends the Progression-Free Survival (PFS) of 4.9 months without an Overall Survival (OS) benefit [5,6]. Furthermore, anlotinib, an oral small-molecular anti-angiogenic agent, was reported to treat platinum-resistant ovarian cancer [7-9]. Therefore, we retrospectively evaluated the efficacy and safety of anlotinib maintenance therapy in patients with newly diagnosed stage III–IV Epithelial Ovarian Cancer (EOC) after completing the recommended cycles of adjuvant chemotherapy.

PATIENTS AND METHODS

Patient Characteristics

From January 2020 to December 2021, a total of 20 patients with newly diagnosed stage III–IV EOC were enrolled from the Affiliated Hospital of Jiujiang University. The baseline characteristics of these patients are described in **Table 1**. The median age at diagnosis was 60.5 years (range, 52-72 years). Pathological diagnosis confirmed that 16 patients had serous carcinoma, 3 patients had endometrioid carcinoma, and 1 patient had mixed serous and endometrioid carcinoma. 12 patients were assessed for BRCA gene mutations (5 patients with mutant BRCA1/2 and 7 patients with wild-type BRCA), while the other 8 patients did not undergo an examination of their BRCA status. All patients were diagnosed with advanced-stage disease (stage III, n=5; stage IV, n=15). 15 (75%) patients showed malignant ascites and received intraperitoneal chemotherapy. 18 patients (90%) underwent cytoreductive surgery. 19 (95%) patients were treated with 6 cycles of chemotherapy (paclitaxel and carboplatin), except for 1 patient who received only 4 cycles of chemotherapy owing to grade ≥ 3 myelosuppression.

Table 1: Baseline characteristics of ovarian cancer patients (n (%)).

Characteristic	n=20 (%)
Age, years	
Median (range)	60.5 (52–72)
ECOG PS, n (%)	
0	4 (20%)
1	7 (35%)
2	9 (45%)
Histology, n (%)	
Serous	16 (80%)
Endometrioid	3 (15%)
Mixed serous and endometrioid	1 (5%)
BRCA status, n (%)	
BRCA 1/2 mutation	5 (25%)
Wild type	7 (35%)
Unknown	8 (40%)
International FIGO stage	
III	5 (25%)
IV	15 (75%)
Malignant ascites	
Yes	15 (75%)
No	5 (25%)
Intraperitoneal chemotherapy	
Yes	15 (75%)
No	5 (25%)
Cytoreductive surgery	
Yes	18 (90%)
No	2 (10%)
Cycles of chemotherapy (paclitaxel and carboplatin)	
4 cycles	1 (5%)
6 cycles	19 (95%)

Treatment and Dose-Adjustment Protocols

Anlotinib (Nanjing Chia Tai Tian Qing Company, Nanjing, China) was taken orally (before breakfast) once daily on days 1-14, every 3 weeks during a cycle. The doses of anlotinib were classified as 12 mg, 10 mg, and 8 mg daily. No chemotherapy or radiotherapy was performed during anlotinib treatment. Anlotinib was taken until disease progression or unacceptable toxicity.

According to the manufacturer's instructions, drug dose-adjustments are permitted based on the levels of adverse reactions, as illustrated in **Table 2**. Adverse reactions were recorded and graded from 0 to 4 according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC) version 4.0.

Table 2: Principle for the adjustment of anlotinib dose.

Levels of adverse reactions (NCI-CTC)	Dose adjustment
Grade 0–2	Drug administration will be continued at the initial dose of 12 mg/day as planned.
Grade 3	Drug administration will be paused, and anlotinib will be continued at the reduced dose of 10 mg/day when the NCI-CTC level is restored to <2 within 2 weeks.

Grade 4	Drug administration will be paused, and anlotinib will be continued at the reduced dose of 8 mg/day when the NCI-CTC level is restored to <2 within 2 weeks. If there is no recovery over 2 weeks, anlotinib will be permanently discontinued.

Response Evaluation Criteria

The primary study outcome was PFS. The objective responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, which were Complete Remission (CR), Partial Remission (PR), Stable Disease (SD), and Progressive Disease (PD). Gynecological examinations were conducted after every 2 cycles of anlotinib treatment and included magnetic resonance and abdominal color ultrasound imaging.

Follow-Up

All patients were followed-up with until disease progression or death. The PFS was calculated from the start of anlotinib administration until disease progression, patient follow-up loss, or death. The end of the follow-up period was December, 31, 2022. The median follow-up time of the entire group was 13.5 months (range, 6.0-21.0 months). No patients were lost to follow-up.

Statistical Analysis

Descriptive statistics were used to describe all participants' clinical characteristics. The Kaplan-Meier method was utilized to evaluate PFS. All statistical analyses were performed using Graph Pad Prism version 7.0 (Graph Pad Software, Inc., San Diego, CA, USA).

Ethics Approval and Consent to Participate

Ethics approval was obtained from the medical ethics committee of Jiujiang University Affiliated Hospital. Informed consent was waived because of the retrospective nature of the study. The study was performed in accordance with the Declaration of Helsinki concerning the ethical principles for medical research.

RESULTS

Clinical Efficacy

Follow-up was completed for all 20 patients with advanced EOC. The best response was evaluated using the RECIST (version 1.1) criteria in all patients enrolled (**Table 3**). Only one patient achieved a CR; 12 patients had a PR, and 6 patients reported SD; meanwhile, 1 patient experienced PD. The ORR and disease control rate (DCR) were 65% and 95%, respectively. The median PFS (mPFS) was 14.8 months (95% confidence interval, 11.5-18.0 months) (**Figure 1**). In addition, the wild-type subgroup showed a tendency toward a prolonged mPFS compared to the BRCA1/2 mutation subgroup (14.8 vs. 11.8 months), but no significant difference was found between them (P=0.3621) (**Figure 2**).

Table 3: Objective response in newly diagnosed EOC patients.

Clinical outcome	No. of patients (%) (n=20)
CR	1 (5%)
PR	12 (60%)
SD	6 (30%)
PD	1 (5%)
ORR (CR+PR)	13 (65%)
DCR (CR+PR+SD)	19 (95%)

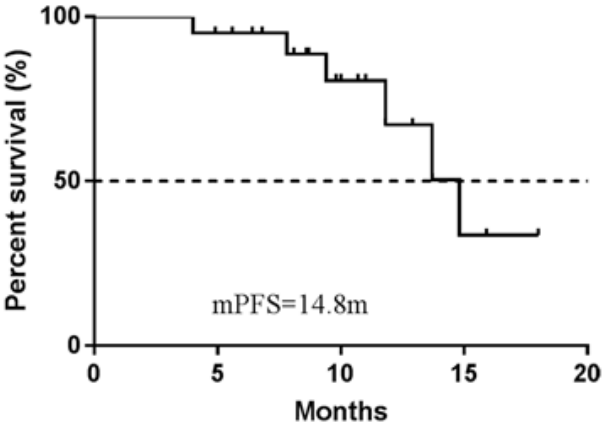

Figure 1: PFS curve of total population.

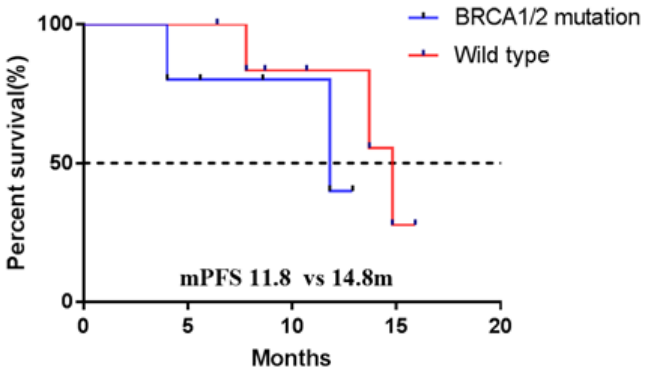

Figure 2: PFS curve of BRCA1/2 mutation and wild type subgroups.

Dose Adjustment

Seven patients (35%) were started on an initial dose of 10 mg/day, but the doses of two patients were reduced to a daily dose of 8 mg owing to grade 3 or 4 side effects. The other 13 patients (65%) began treatment with 12 mg/day, but five required a dose reduction to 10 mg/day due to grade 3 or 4 adverse events.

Adverse Effects

Adverse reactions were assessed from the start of anlotinib treatment until disease progression or the last follow-up date. The anlotinib-related adverse effects included hypertension, proteinuria, fatigue, hand-foot syndrome, and leukopenia (**Table 4**). The grade 3 toxicities were hypertension (15%), fatigue (10%), leukopenia (5%), and proteinuria (5%). Except for one case of grade 4 hypertension and one case of grade 4 leukopenia, no grade 4 toxicities were recorded. No deaths associated with anlotinib were observed.

Table 4: Anlotinib-related adverse effects (n (%)).

Adverse effects	No. of patients				Total
	Grade 1	Grade 2	Grade 3	Grade 4	
Hypertension	7 (35%)	4 (20%)	3 (15%)	1 (5%)	15 (75%)

Proteinuria	2 (10%)	1 (5%)	1 (5%)	0	4 (20%)
Fatigue	6 (30%)	3 (15%)	2 (10%)	0	11 (55%)
Hand-foot syndrome	5 (25%)	2 (10%)	0	0	7 (35%)
Leukopenia	4 (20%)	2 (10%)	1 (5%)	1 (5%)	8 (40%)

DISCUSSION

Although chemotherapy is initially effective for the treatment of EOC, nearly all advanced-disease patients eventually relapse and become resistant to platinum-based therapies within 5 years. Therefore, how to extend the relapse-free interval is of great clinical significance in improving the prognosis of ovarian cancer patients. Currently, maintenance therapy has emerged as a novel treatment strategy for advanced ovarian cancer patients, i.e., PARP inhibitors (olaparib, rucaparib, and niraparib) and anti-angiogenesis therapies (bevacizumab) [10].

In the PRIMA study, the mPFS of the niraparib group was markedly longer than that of the placebo group (13.8 vs. 8.2 months) in the overall population. Subgroup analysis revealed that the mPFS was 22.1 and 21.9 months for the BRCA-mutation and Homologous-Recombination Deficiency (HRD) groups, respectively. Of note, the Homologous-Recombination Proficiency (HRP) subgroup of ovarian cancer patients accounted for 65.7% of all patients with an mPFS of 8.1 months [11]. In both GOG-0218 and ICON-7, first-line bevacizumab maintenance only prolonged the mPFS by about 4.0 months for patients with advanced ovarian cancer, indicating a limited efficacy of bevacizumab maintenance in extending the relapse-free survival [12]. The phase III study of PAOLA-1 reported that olaparib plus bevacizumab greatly improved the mPFS in comparison to bevacizumab alone in ovarian cancer patients with HRD (37.2 vs. 17.7 months), the prevalence of which was about 50% [13]. However, about 50% of ovarian cancer cases had a BRCA-wild type and HRP status, and these patients only marginally benefited from PARP inhibitor maintenance therapy, with an mPFS of about 5 months [14,15]. Thus, there is an unmet need to extend the relapse-free interval for patients with ovarian cancer, especially with a BRCA-wild type and HRP status.

Anlotinib is an oral multi-targeted tyrosine kinase receptor inhibitor that can inhibit tumor angiogenesis and growth in a wide range of cancers. At present, the National Medical Production Administration of China has approved anlotinib for posterior-line treatment of advanced small-cell lung cancer, non-small-cell lung cancer, esophageal carcinoma, and soft tissue sarcoma [16-19]. In 2015, anlotinib was approved by the U.S. Food and Drug Administration as an orphan drug for use in ovarian cancer treatment. Zhang et al. reported that anlotinib monotherapy resulted in a marked PR and a PFS of >4 months in an elderly patient with advanced EOC after the failure of multiple-line chemotherapy [8]. In a retrospective observational study, anlotinib alone, anlotinib combined with chemotherapy, or the anti-programmed cell death protein 1 therapeutic pembrolizumab was administered to 38 patients with platinum-resistant or refractory EOC. The mPFS and median OS were 7.7 and 16.5 months, respectively. Among them, 17 patients receiving anlotinib monotherapy achieved an mPFS of 7.7 months. The ORR was 42.1%, while the DCR was 86.8% [20]. A prospective, single-arm phase II study documented an ORR of 25% and a DCR of 100% for a group of platinum-resistant EOC patients receiving anlotinib plus pemetrexed [21]. The results indicated that anlotinib exhibited moderate clinical outcomes for platinum-resistant EOC. However, the subjects in these studies had chemo-resistant ovarian carcinoma.

In this retrospective study, we first explored the effect of anlotinib maintenance on the relapse-free interval of newly diagnosed EOC patients. The ORR was 65%, and the DCR was 95%. Among all cases, the mPFS time was 14.8 months, which is comparable to the effect of niraparib (13.8 months) in the PRIMA study. Furthermore, a subgroup analysis revealed that the mPFS was 11.8 months in the BRCA1/2-mutation subgroup. Relatively speaking, anlotinib maintenance was less effective against BRCA1/2-mutation EOC than niraparib maintenance (22.1 months). However, anlotinib triggered a satisfactory clinical efficacy for patients with BRCA wild-type EOC, with an mPFS of 14.8 months, which was considerably better than that of PRAP inhibitors (about 5 months). Additionally, 35% of all patients experienced a dose reduction due to grade III-IV toxicities, which was manageable and tolerable.

This study has some limitations that need to be addressed. First, this was a retrospective study, which is a limitation. Second, the overall sample size of this study was small, which needs to be expanded further to validate the therapeutic findings. Finally, not all patients had their BRCA-mutation status tested. However, we believe that this study can provide a reference for anlotinib maintenance therapy in newly diagnosed ovarian cancer patients.

CONCLUSION

In conclusion, first-line anlotinib maintenance therapy might be a promising agent for ovarian cancer patients after they complete the recommend cycles of chemotherapy, especially for BRCA wild-type EOC patients with manageable toxicities. Further investigations are warranted to confirm the clinical outcome of anlotinib maintenance treatment following adjuvant chemotherapy in the treatment of newly diagnosed EOC patients.

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AUTHOR'S CONTRIBUTIONS

D.J. contributed to the study conception and design. Material preparation, data collection and analysis were performed by D.J. and L.Z. All authors read and approved the final manuscript.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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COMPETING INTERESTS STATEMENT

The authors have not disclosed any competing interests.

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